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A New Vista of Opportunity in Diabetes Management: Natural Product-Based β-cell Preservation

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ABSTRACT

A defining characteristic of diabetes is β-cell failure, in which β-cells cannot modulate insulin secretion to compensate for escalating insulin resistance, pushing forward disease development. However, functional β-cell preservation is implicated in maintenance/restoration of β-cell mass (survival/proliferation), identity, maturity, insulin synthesis/secretion, and resistance to cell death. Targeting these related processes is a promising approach for treating and curing diabetes. This review provides a comprehensive overview of a natural product-based β-cell-centric approach to diabetes treatment, focusing on molecular mechanisms, natural inhibitors, and clinical potential. Relevant publications from 2002 to 2025 were retrieved through a systematic database search of PubMed, Web of Science, and Google Scholar. As a result of the search, 16 natural compounds, belonging to 5 major structural classes, polyynes, (iso)flavonoids, alkaloids, aliphatic amino alcohols, and phenolics, were chosen for discussion in this review based on their β-cell-modulatory properties. In parallel, thirteen β-cell-relevant molecular targets are identified and discussed: positive regulators of β-cells (PI3K, NKX6.1, PDX1, P2RY1, S1P receptors, P2Y1 receptors, antioxidant enzymes, TEAD1 and SIRT1), and negative regulators (MST1, BACH2, PHLPP1 and PDIA4). Furthermore, key challenges, use dosage, treatment duration and specificity, target identification, and likely side effects of the above compounds are discussed. Thistle, *Ophiocordyceps sinensis*, *Peganum harmala*, *Bidens pilosa*, *Curcuma longa*, vegetables, fruits, soybean, teas, coffee, cocoa, wines, and their compounds (silymarin, quercetin, genistein, harmine, polyyynes, phenolics, curcumin, and epigallocatechin 3-gallate) are generally recognized as safe for human consumption. Further studies, including in-depth animal models and human studies in compounds, are presented along with an assessment of efficacy and safety. A combination of β-cell-modulatory nutraceuticals, phytocompounds, and/or drugs may represent a futuristic approach to treating diabetes by preserving β cells, offering new anti-diabetic remedies. In conclusion, the natural compounds discussed in this review are readily available in everyday life and show promise as new nutraceuticals and/or pharmaceuticals for achieving β-cell homeostasis and glycemic control in diabetes management.

Abbreviations: AGI, α-glucosidase inhibitor; AKT, Protein kinase B; BACH2, BTB domain and CNC homolog 2; DPP4, dipeptidyl peptidase 4; DYRK1A, dual-specificity tyrosine phosphorylation-regulated kinase 1A; EGCG, epigallocatechin 3-gallate; ETC C1, electron transport chain complex 1; GLP1, glucagon like protein 1; GLUT2, glucose transporter 2; GPCR, G protein-coupled receptors; GSIS, glucose-stimulated insulin secretion; GSK3, glycogen synthase kinase-3; IP3, inositol triphosphate; JNK1, c-Jun N-terminal kinases 1; MARE, MAF recognition element; MetS, metabolic syndrome; MKK7, mitogen-activated protein kinase kinase 7; MST1, macrophage stimulating 1; mTORC, mammalian target of rapamycin complex; NKX6.1, NK6 homeobox 1; NOX, NADPH oxidase; OAA, oral anti-diabetic agent; P2Y, purinergic receptor; PDIA4, protein disulfide isomerase A4; PDK1, phosphatidylinositol triphosphate-dependent protein kinase 1; PDX1, pancreatic and duodenal homeobox 1; PHLPP1, PH domain leucine-rich repeat protein phosphatase; PIP2, phosphatidylinositol biphosphate; PIP3, phosphatidylinositol triphosphate; PTPN2, protein tyrosine phosphatases non-receptor type 2; ROS, reactive oxygen species; S1P, sphingosine 1 phosphate; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SIRT1, sirtuin 1; SREBP1c, sterol regulatory element-binding protein 1c; STZ, streptozocin; T1D, type 1 diabetes; T2D, type 2 diabetes; TAK1, transforming growth factor β-activated kinase 1; TEAD1, TEA domain transcription factor 1; TRAF6, TNF receptor associated factor 6.

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Highlights

- Preservation of β-cell number and function is the key to curing diabetes.
- Natural products are emerging as a novel approach to preserve functional β-cells, leading to diabetes.

1 | Introduction

Aretaeus of Cappadocia, the renowned Greek physician, identified diabetes around two millennia ago. However, this old disease remains incurable. More than 90% of diabetes sufferers are diagnosed with type 2 diabetes (T2D), while 10% or less are found to have type 1 diabetes or other types (Kuo, Hsu, et al. 2021). T2D is characterized by two fundamental deficiencies, β-cell failure and insulin resistance, resulting in dysregulation of glucose as well as protein and lipids (Minkova et al. 2022; Yabe et al. 2015; Galicia-Garcia et al. 2020). Genetic and environmental factors are major causes of this disease (Li et al. 2020; Cerf 2013; Yang et al. 2013). In 2024, the International Diabetes Federation reported that diabetes likely afflicts 589 million people and causes 5 million deaths every year worldwide (Magliano et al. 2025; Tseng et al. 2023). Of which, China (148 million), India (90 million), the United States (39 million), Pakistan (35 million), Indonesia (20 million), and Brazil (17 million) are the top 6 countries that have the largest number of diabetes patients in the world (Magliano et al. 2025).

However, currently commonly administered orthodox oral antidiabetic drugs are less than ideal in terms of efficacy and have several side effects that lead to microvascular and macrovascular complications. There is, therefore, a great demand for novel diabetes therapies.

During T2D development, insulin resistance increases over time while the mass and function of β-cells simultaneously decline (Dludla et al. 2023; Karaca et al. 2009; Leahy 2005). Schwartz et al. reported that at least 11 pathways in various organs and tissues are involved in insulin resistance and the failure of β-cells (S. S. Schwartz and Herman 2024). Current anti-diabetic drugs that target some of the above pathways can maintain glycemic control for many years. Unfortunately, although glycemic homeostasis is able to reduce diabetic complications, this symptom management is unable to reverse or cure diabetes. One of the key methods by which diabetes can be reversed/cured lies in improving beta cells that are progressively exhausted due to overnutrition (T2D) or heading toward death due to attacks by autoimmune cells (type 1 diabetes (T1D)). A growing body of evidence supports a major shift to β-cell-centric approaches in diabetes treatment, in contrast to the prior glucose-centric approach (Saisho 2020; J. Schwartz et al. 2016).

According to the World Health Organization, 80% of the world population uses complementary and alternative medicine (including herbal medicines, acupuncture, moxibustion, and other therapies) for primary health care (Hoenders et al. 2024). Over 1200 plants are known to have anti-diabetic activities. Therefore, plants are an important area of investigation for anti-diabetic health foods and remedies with respect to efficacy, mechanisms, phytochemistry, and safety (Willcox et al. 2021; Smoak et al. 2021). This review looks holistically at the overall state of the art in natural product-based β-cell preservation as a strategy for diabetes management and offers perspectives for future development. We first address the molecules and pathways involving β-cell mass and function. Then, we look at five classes of natural compounds with anti-diabetic activities, from their molecular basis to their health benefits. After that, we delineate preclinical studies, clinical studies, and molecular targets of natural compounds in β-cell preservation and diabetes. We also discuss the pros and cons of using these natural products as anti-diabetic nutraceuticals and/or pharmaceuticals. Although there are over 30 classes of anti-diabetic drugs, accumulating evidence suggests that dietary compounds target molecules and pathways involved in β-cell preservation, representing a new vista in diabetes management. Therefore, this review provides a new outlook, highlighting the emergence and merits of scientific research on dietary interventions for diabetes.

2 | Review Methodology

A systematic literature search was conducted among the major scientific research databases, PubMed, Web of Science, and Google Scholar. Key terms such as "β-cell," "death," "proliferation," "gene" and/or "natural product" were used. As outlined in Figure 1, publications between 2002 and 2025 were retrieved. These pieces of research were then evaluated by hand and trimmed with respect to their impact and the novelty of the selected therapeutic molecules, functions, mechanisms, clinical potential, and natural product-based inhibitors of the therapeutic molecules implicated in β-cell preservation and diabetes.

3 | β-Cell Preservation and Diabetes: A Brief Overview

Pancreatic β-cells are the exclusive regulators of insulin synthesis and secretion and are central to glucose homeostasis and other metabolic processes (S. S. Schwartz et al. 2016). β-cell dysfunction and loss, a cardinal hallmark for diabetes, are driven by diabetogenic stimuli, metabolic stress, immunity, and inflammation, leading to insufficient insulin production and/or release and ultimately hyperglycemia (Cerf 2013). Functional β-cell preservation maintains β-cell mass, function, cellular identity, and resilience against diabetogenic stimuli (Efrat 2019; Nair et al. 2020). Clinical and experimental evidence indicate that preserving functional β-cells improves metabolic control and delays disease progression across multiple forms of diabetes (Saisho 2020).

Schwartz et al. coined the term "Egregious 11" to represent 11 metabolic pathways in the pancreas (β-cells and α-cells) and extra-pancreatic tissues (colon/microbiome, gastrointestinal tract, liver, adipose tissue, muscle, brain, kidney, and immune system) (S. S. Schwartz et al. 2016). This model illustrates the involvement of interlocking pathways in insulin deficiency and insulin resistance and their participation in glycemic

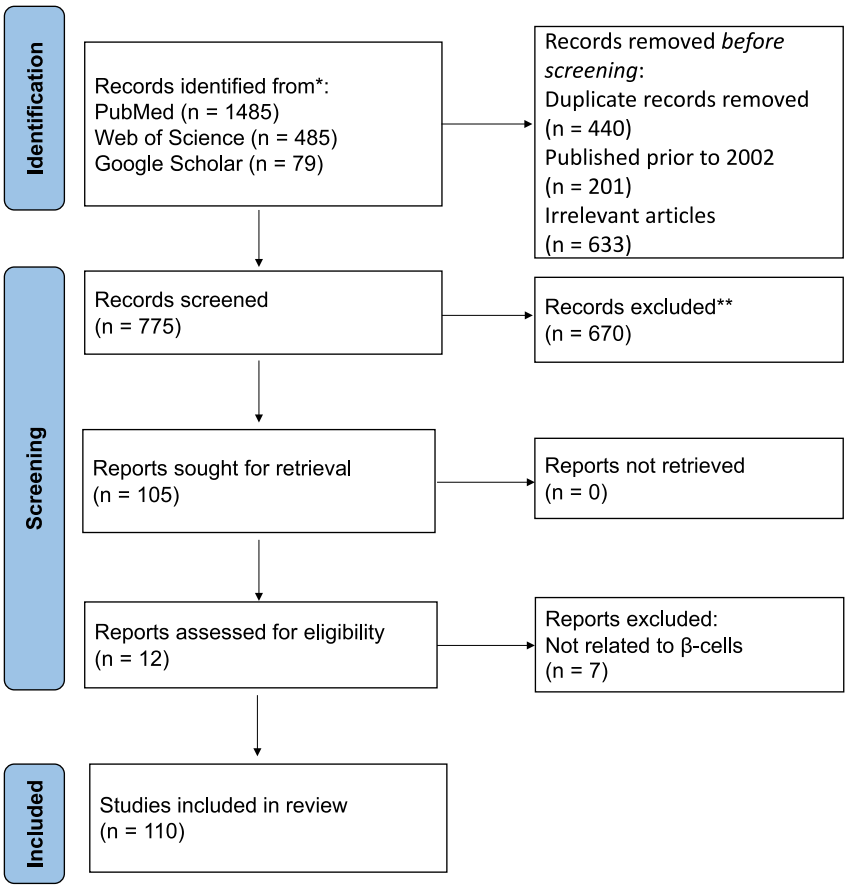


FIGURE 1 | PRISMA flowchart diagram showing the identification of studies through a literature search against public databases.

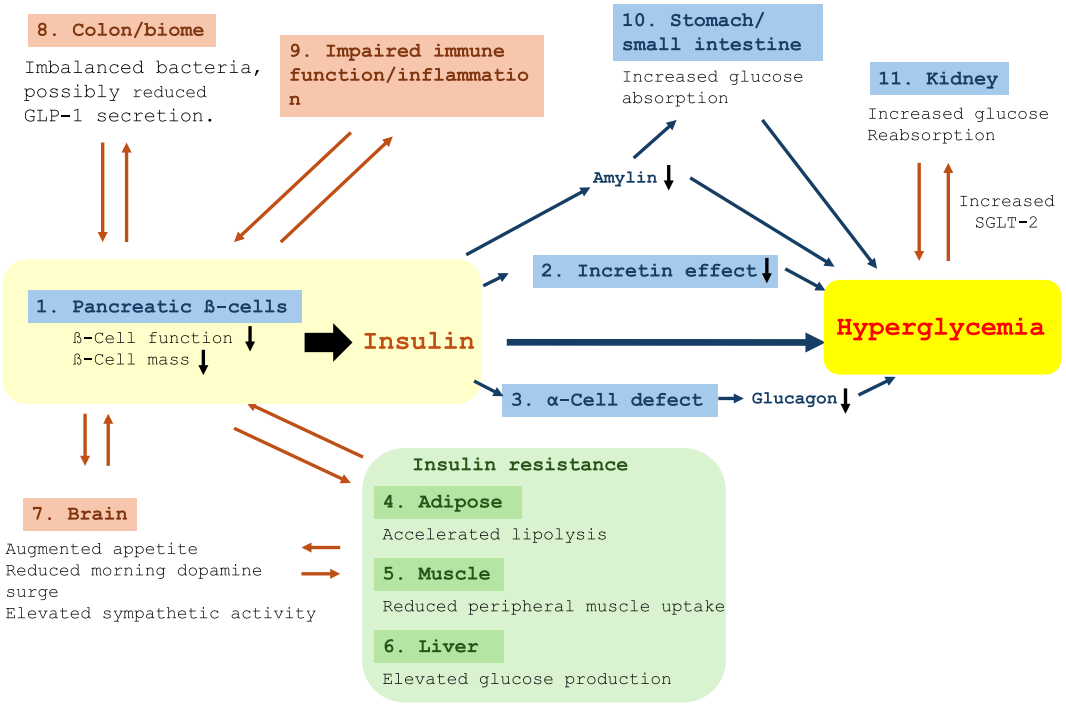


FIGURE 2 | A β-cell-centric model. In this model, β-cell dysfunction and loss are thought to be a major cause of diabetes. Eleven distinct but entwined pathophysiologic pathways, as denoted from 1 to 11, may contribute to β-cell dysfunction that results in hyperglycemia, as published (S. S. Schwartz et al. 2016).

dysregulation and T2D development (Figure 2). Six upstream contributors to beta cell dysfunction include insulin resistance in the adipose tissue, liver, and skeletal muscle, as well as dysregulation in the brain, gut, and immune system. Five downstream effects of hyperglycemia resulting from this damage include decreased insulin production, reduced incretin effects and amylin levels, increased glucagon secretion, and increased renal glucose reabsorption. Importantly, β-cell failure represents the converging node of these mechanisms, as compensation for insulin resistance becomes unsustainable when β-cell mass and function decline. Targeted therapies that manipulate these 11 pathophysiologic mechanisms may provide the most benefit to diabetes patients. Currently, oral antidiabetic agents (OAA) can maintain glycemic homeostasis, a common goal in therapies for T2D and its complications. Aside from insulin injection, there are tens of OAA, such as insulin sensitizers, insulin releasers, α-glucosidase inhibitors (AGI), incretin-based drugs (glucagon-like protein 1 (GLP1) mimetics and dipeptidyl peptidase 4 (DPP4) inhibitors), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and so on (Figure 3). Among OAA, insulin sensitizers like rosiglitazone, and pioglitazone and metformin, are able to reduce insulin resistance directly and, thus, lower blood glucose. In contrast, AGI can reduce glucose (re)absorption via the intestines and SGLT2i can act similarly via the kidneys (Egan et al. 2003; Jones 2011). Although insulin releasers can boost β-cell insulin secretion for glucose reduction, they risk exhausting β-cells (Chang et al. 2013; Wright et al. 2002). Of note, GLP1 analogs and DPP4 inhibitors can lower blood glucose through multiple actions, including reduced glucagon, increased insulin, and reduction of gastric emptying (Parkes et al. 2012). However, the current OAA have several limitations (Chang et al. 2013). First, most OAA target the pathways in the extra-pancreatic tissues but not the islets and fail to directly preserve β-cell mass or long-term functionality. Next, prolonged stimulation of insulin secretagogues may further accelerate β-cell exhaustion. Finally, GLP1 mimetics have been documented to have beneficial effects on β-cells in animal models but remain to be proven clinically. As a result, effective glycemic control cannot translate into disease reversal, underscoring the need for β-cell–centric therapeutic strategies.

Aside from insulin resistance, loss of β-cell number and function is pivotal in the development of T2D. Therefore, the preservation and even the restoration of functional β-cells is a promising approach for the treatment and complet. alleviation of diabetes (Kuo, Hsu, et al. 2021). Diabetogenic stimuli always induce cell stress, for example, ER stress and oxidative stress, in pancreatic β-cells, leading to cell dysfunction and death, that is, β-cell failure (Efrat 2019). Accumulating studies show that β-cell mass is lowered by 20%–50% in those with pre-diabetes, and this mass is further reduced to 40%–60% in new-onset diabetes. The β-cell mass then continues to decline at a rate of approximately 5% per year. Eventually, in late-stage diabetes, less than 10% of β-cell function remains (Wysham and Shubrook 2020; Cohrs et al. 2020; Saisho 2020). Considerable data suggest that preserving β-cell number and function can reverse T2D (Suleiman et al. 2022). Furthermore, modulation of β-cell growth, proliferation, survival and death, differentiation from β-cell precursors, and regulation of β-cell homeostasis all contribute to β-cell homeostasis and have emerged as attractive strategies for diabetes (Figure 4). However, in diabetes, β-cell loss often exceeds their replenishment. High glucose levels can easily cause cell death in pancreatic β-cells (Apaya et al. 2020; Kuo, Hsu, et al. 2021). Such glucose toxicity is thought to induce oxidative stress (e.g., ROS) and, in turn, impair β-cell survival and function in animals (Kuo, Hsu, et al. 2021) and in humans (Karaca et al. 2009). Therefore, β-cell impairment is aggravated by dysregulation of blood glucose and other metabolites. β-cell replication, differentiation, and maturation are relatively slow in

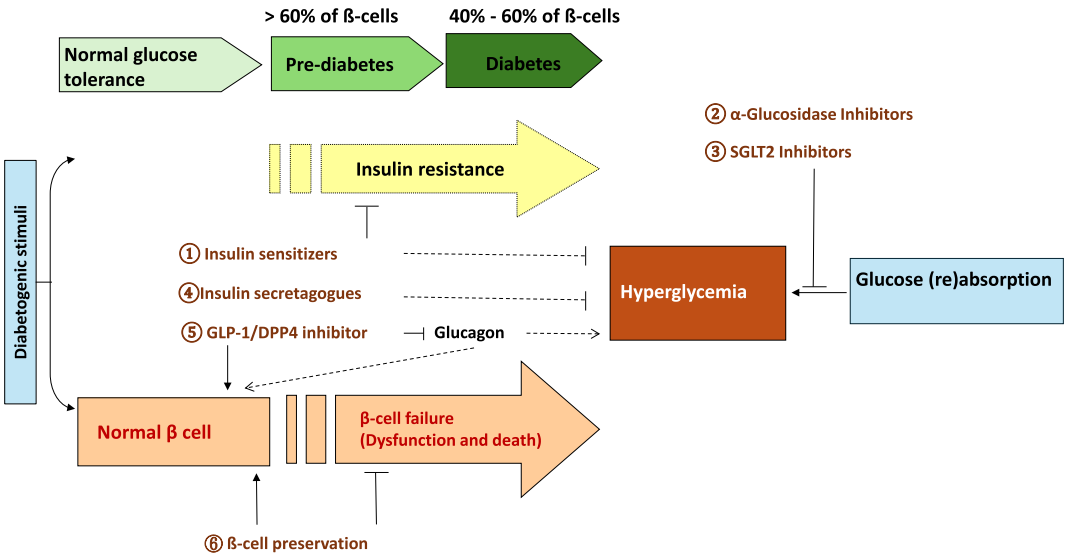


FIGURE 3 | Etiology, development, and current therapies for T2D (adapted from Chang et al. 2013). The main players in insulin resistance development and impaired glucose tolerance leading to diabetes are genetic and environmental factors. Under regular glucose tolerance conditions, β-cells secrete insulin in response to large increases in glucose after a meal. Upon impaired glucose tolerance, β-cells overfunction to compensate for increasing insulin resistance. In case this compensation fails, prediabetes progresses to full-blown diabetes. As indicated, the OAAs can control glycemia via multiple mechanisms (Chang et al. 2013). Unfortunately, no drugs that can stop β-cell failure are currently clinically available.

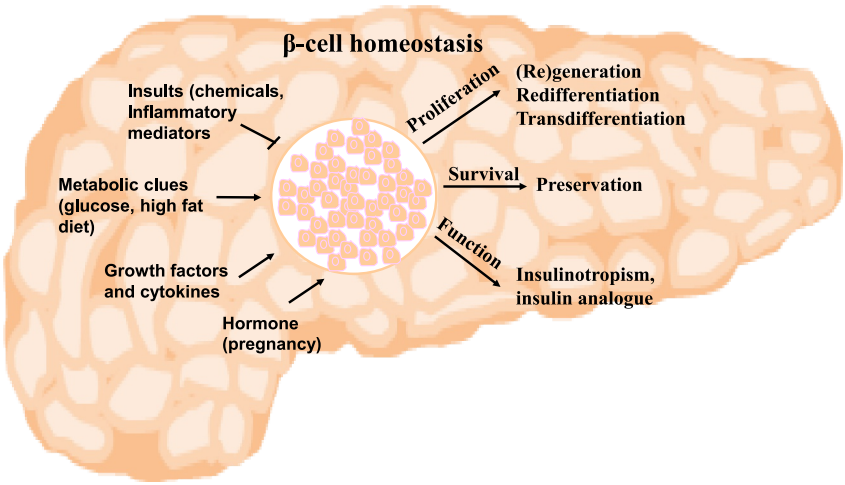


FIGURE 4 | Modes of action that modulate β-cell homeostasis. The β-cell homeostasis is modulated by β-cell proliferation, survival, and function, resulting in β-cell (re)generation, preservation, and insulin production and secretion, respectively. Metabolic indicators (e.g., glucose, a high-fat diet), growth factors, cytokines, and hormonal changes can increase β-cell mass and function, whereas diabetogenic stimuli (e.g., chemicals, inflammatory mediators, ER stress, oxidative stress) are able to compromise β-cell mass and function.

diabetic hosts compared to those in pre-birth embryos, where replication is exponential (Apaya et al. 2020). It has been estimated to be 2%–2.5% in neonatal fetuses, 0.2%–0.5% in adolescents, and 0.1%–0.2% in adults, respectively (Gregg et al. 2012; Meier et al. 2008; Apaya et al. 2020). Several studies indicate that β-cell (re)generation in human adults is modest. Various metabolic marks, growth factors, cytokines, and hormones have been documented to regulate proliferation, survival, and function in β-cells and preserve their homeostasis (Apaya et al. 2020). Transcriptional factors, kinases, signaling molecules, oxidative stress regulators, death ligands/receptors/adaptors, and so on, can serve as downstream factors that aid in maintaining β-cell homeostasis. Notably, a β-cell-centric strategy for treating diabetes has emerged as a mainstay of diabetes prophylaxis, therapy, and cure (Leahy et al. 2010; S. S. Schwartz et al. 2016). However, there are currently no clinically effective anti-diabetes drugs that preserve β-cell mass and functionality.

4 | Key Players and Their Pathways That Control β-cell Homeostasis

Due to the unmet need for novel T2D treatments, new approaches to treat and cure T2D are in high demand (Chang et al. 2013). Interestingly, preserving functional β-cells as a T2D therapy has increasingly been recognized since 2009 (Karaca et al. 2009; Leahy et al. 2010). Studies in both humans and animals have suggested that a T2D characteristic that drives disease development is a decline in functional β-cell mass resulting in loss of modulation of insulin secretion to compensate for increasing insulin resistance (Figure 2) (Karaca et al. 2009; Leahy et al. 2010). Both preclinical and clinical data have shown a continued decline in β-cell function and mass (Nair et al. 2020), leading to T2D progression (J. Shao et al. 2006). Mounting evidence suggests the possibility of stabilizing, delaying, and even reversing this decline, especially at the early stages of diabetes (Kuo, Hsu, et al. 2021; Nair et al. 2020), suggesting that preserving functional β-cell mass is crucial for preventing and curing T2D (Defronzo 2009; Nair et al. 2020; S. S. Schwartz et al. 2016).

It is highly plausible that, like other cells, β-cell growth and survival can be orchestrated by multiple genes. Elucidation of the major players involved in β-cell preservation and increase is crucial for understanding β-cell biology and T2D, and also for developing novel curative strategies for the disease. It has been reported that the homeostasis of β-cells is regulated by potential molecular targets including macrophage stimulating 1 (MST1) (Ardestani et al. 2014), glycogen synthase kinase 3 (GSK3) (Sacco et al. 2019), sphingosine-1-phosphate (S1P) receptors (Liu et al. 2021; Q. He et al. 2021), phosphatidylinositol 3-kinases (PI3K) (Camaya et al. 2022), NK6 homeobox 1 (NKX6.1) (Aigha and Abdelalim 2020), pancreatic and duodenal homeobox 1 (PDX1) (Sacco et al. 2019; Siwan et al. 2024), P2Y1 (Marcheva et al. 2022), PH domain leucine-rich repeat protein phosphatase 1 (PHLPP1) (Lupse et al. 2021), dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) (Lu et al. 2019), TEAD1 (J. Lee et al. 2024), sirtuin 1 (SIRT1) (J. H. Lee et al. 2009; Wu et al. 2012), antioxidant enzymes (Lei and Vatamaniuk 2011; Lei et al. 2016), BTB domain and CNC homolog 2 (BACH2) (Son et al. 2021), and protein disulfide isomerase A4 (PDIA4) (Kuo, Hsu, et al. 2021) (Figure 5). The functions of the foregoing molecules are summarized in Table 1 and described as follows.

4.1 | Key Players and Their Pathways That Control β-Cell Identity, Proliferation, and Function

PI3K, NKX6.1, PDX1, S1P receptors, P2Y1, antioxidant enzymes, TEAD1, and SIRT1 promote β-cell growth, that is, proliferation and (re)differentiation. PDX1, predominantly expressed in pancreatic and duodenal cells, is a key transcriptional factor that orchestrates β-cell function, β-cell survival (Fujimoto and Polonsky 2009), β-cell identity (Gao et al. 2014), and pancreatic islet development in animals (Siwan et al. 2024).

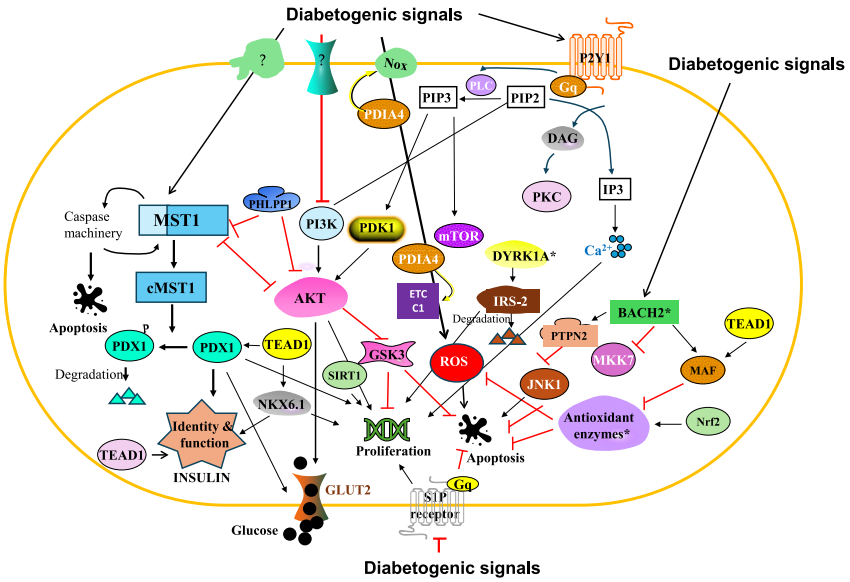


FIGURE 5 | A schema showing the key genes implicated in β-cell identity, function, proliferation, and death. PI3K, NKX6.1, PDX1, P2RY1, S1P receptors, P2Y1 receptors, antioxidant enzymes, TEAD1, and SIRT1 are positive regulators of β-cell identity, proliferation, and/or function. In contrast, MST1, BACH2, PHLPP1, and PDIA4 are negative regulators of β-cell identity, proliferation, and/or function. Their signaling pathways are summarized and discussed in this review. The asterisk marks (*) represent a discrepancy in the role of BACH2, DYRK1A, and antioxidant enzymes in β-cells, as revealed in the literature. The black arrows and red lines denote promotion and inhibition, respectively. Diabetogenic signals impair β-cells via the aforementioned molecules and pathways.

However, phosphorylated PDX1 undergoes ubiquitin-dependent degradation and, subsequently, loss of function. Therefore, the underlying mechanism of PDX1 involves the promotion of caspase-dependent apoptosis and PDX1-dependent dysfunction in β-cells (PDX1, Figure 5) (Ardestani et al. 2014).

PI3K is a heterodimer comprising a regulatory subunit, p85, and a catalytic subunit, p110. This lipid kinase, initially identified as an oncogene, is widely expressed in different cell types (Camaya et al. 2022). It converts phosphatidylinositol biphosphate (PIP2) into phosphatidylinositol triphosphate (PIP3). PIP3 serves as a secondary messenger that binds and activates PI3K's downstream molecules, phosphatidylinositol triphosphate-dependent protein kinase 1 (PDK1), and mammalian target of rapamycin complex (mTORC). mTOR and PDK1 can phosphorylate protein kinase B (AKT), resulting in the upregulation of proteins governing growth, proliferation, and survival in β-cells (Camaya et al. 2022). Likewise, PDK1 positively regulates β-cell mass (Hashimoto et al. 2006). Consequently, the PI3K/PDK1/AKT cascade increases β-cell mass and function (PI3K, Figure 5) (Camaya et al. 2022). NKX6.1, a transcriptional factor, is exclusively expressed in β-cells. It has been shown to dictate pancreatic β-cell development, identity, and division (Aigha and Abdelalim 2020). It is thought that NKX6.1 contributes to pancreatic development at the early stage, and adult β-cell function (NKX6.1, Figure 5) (Aigha and Abdelalim 2020).

DYRK1A, one of five DYRK serine/threonine kinases, is expressed in the brain, immune cells, islet cells, etc. (Lindberg and Meijer 2021). Lindberg and Meijer stated that DYRK1A possesses multiple functions in development and growth. Mutations in humans and animals were found to cause nervous diseases, infections, immune diseases, cancer, and diabetes (Lindberg and Meijer 2021). One study reported that mice with DYRK1A haploinsufficiency had a low abundance of functional β-cells (Rachdi et al. 2014). Contrastingly, mice expressing a DYRK1A transgene showed reduced glucose levels, elevated insulin levels, and better glucose tolerance. Furthermore, the transgenic mice also had higher β-cell mass in the pancreas (Rachdi et al. 2014). However, another piece of research indicated that overexpression of DYRK1A in transgenic mice augmented β-cell failure via phosphorylation and degradation of IRS-2 (DYRK1A, Figure 5) (Lu et al. 2019). The reasons for the difference between the two studies are not clear. The difference may perhaps be ascribed to the specificity of the transgenic promoters and/or the expression level of the transgene in mice. However, data obtained from the inhibitors of DYRK1A argued that DYRK1A promoted β-cell failure (Bertrand et al. 2025; Dirice et al. 2016).

4.2 | Key Players and Their Pathways That Control β-Cell Life/Death and Function

Reactive oxygen species (ROS) are generally believed to be essential secondary messengers for cell survival (Mittler 2017). However, ROS acts dichotomously on different cells. That is to say, with regard to ROS, a little is a good thing, whereas too much is deleterious (Wei et al. 2023). Multiple pathways are responsible for ROS generation and elimination in eukaryotic cells. Mitochondria, accounting for 90% of cellular ROS, and NADPH oxidase are the two main pathways for ROS generation (ROS, Figure 5). In contrast, glutathione peroxidase 1 (GPX1), superoxide dismutase 1/2/3 (SOD1/2/3), catalase and thioredoxin are the major antioxidant enzymes that eliminate ROS (Antioxidant enzymes, Figure 5) (Lei and Vatamaniuk 2011). Notably, islet-specific overexpression of GPX1, SOD1/2/3,

TABLE 1 | List of key molecular that control β-cell homeostasis.

Molecule	Function	β-cell identity/ maturity	β-cell mass/ function	ROS production/ apoptosis	Scientific evidence
PDX1	β-cell lineage transcription factor; insulin gene regulation	Yes; direct maintenance of β-cell identity and differentiation	Yes; promotion of insulin biosynthesis and survival	Yes; inhibition of apoptosis	PDX1 loss caused β-cell apoptosis and function in mice (Gao et al. 2014) and humans (Abreu et al. 2021)
MAFA	β -cell maturity transcription factor; glucose-stimulated insulin secretion (GSIS)	Yes; a marker of mature β-cells	Yes; promotion of GSIS	No	Co-expression of MAFA and PDX1 engaged human α- or γ-cells into glucose-dependent insulin-secreted pseudoislets which reversed mouse diabetes via transplantation (Furuyama et al. 2019)
NKX6.1	β-cell development and fate determination	Yes; preservation of β-cell identity	Yes; promotion of GSIS and proliferation	No	NKX6.1 regulated β-cell identity, function, and proliferation in rodent and human islets (Aigha and Abdelalim 2020)
IRS/PI3K/ PDK1/AKT	Insulin signaling, growth, and survival	Indirect role	Yes; promotion of survival and adaptive mass expansion	Yes; inhibition of apoptosis	β-cell-specific PDK1 deletion caused diabetes due to β-cell loss (Hashimoto et al. 2006); overexpression of the constitutively active Akt1 in β-cells induced an increase in β-cell size and total islet mass, which protected mice against streptozotocin-induced diabetes (Camaya et al. 2022)
TEAD1	Transcriptional co-factor regulating maturity	Yes; direct maintenance of adult β-cell maturity	Yes; promotion of function and proliferation	No	TEAD1 regulated the PDX1, NKX6.1, and MAFA transcriptional programs in adult mouse β-cells. (J. Lee et al. 2024)
SIRT1	NAD^+-dependent deacetylase; stress response	Indirect role	Yes; promotion of survival and function	No	SIRT1 overexpression or activation protected β-cells from cytokine-induced apoptosis (Wu et al. 2012) or hyperglycemia-induced apoptosis (Lv et al. 2021)
S1P/S1P receptors	Lipid signaling; survival/proliferation	Indirect role	Yes; promotion of proliferation and survival	No	S1P and fingolimod enhanced β-cell mass and function in diabetic mouse and primate models (Y. He

(Continues)

TABLE 1 | (Continued)

Molecule	Function	β-cell identity/ maturity	β-cell mass/ function	ROS production/ apoptosis	Scientific evidence
					et al. 2019; Y. J. Wang et al. 2022)
P2Y receptors	Purinergic GPCR; Ca^{2+} signaling	No	Yes; promotion of insulin secretion	No	Activation of P2Y receptors improved glucose tolerance and GSIS (Mesto et al. 2022; Marcheva et al. 2022)
DYRK1A	Cell-cycle and transcriptional regulator	No	Yes; inhibition of β-cell proliferation and function	No	DYRK1A inhibitors stimulated β-cell proliferation in human (Dirice et al. 2016) and rat (Bertrand et al. 2025)
NRF2 pathway	Antioxidant transcriptional regulator	Indirect role	Yes; promotion of stress resilience and survival	Yes, reduction of ROS injury	NRF2-dependent antioxidant responses protected β-cells from oxidative damage (Baumel-Alterzon et al. 2022)
MST1	Stress-activated pro-apoptotic kinase	No	No	Yes; induction of mitochondrial apoptosis, and PDX1 degradation	MST1 activation drived β-cell apoptosis; inhibition restores survival and glycemia (Ardestani et al. 2014)
PHLPP1	AKT/MST1 phosphatase	No	Yes; negative regulation of β-cell function	Yes; suppression of AKT pro-survival signaling and activation of MST1 pro-apoptosis	PHLPP1 deletion rescued β-cell survival and normoglycemia in db/db mice (Lupse et al. 2022)
PDIA4	ER oxidoreductase; redox regulation	No	Yes; negative regulation of β-cell function	Yes; promotion of mitochondrial and NOX-derived ROS	PDIA4 knockout/ inhibition preserved β-cell function and reverses diabetes in mice (Kuo, Hsu, et al. 2021; Tseng et al. 2023)
BACH2	Stress/apoptosis transcriptional regulator	Controversial role	Controversial role	Yes; modulation of oxidative stress and apoptosis	BACH2 regulated β-cell apoptosis and antioxidant gene repression in T1D/T2D models (Son et al. 2021)
GSK3 (α/β)	Ser/Thr kinase regulating metabolism and survival	Indirect role	Controversial role	Controversial role	GSIS of beta cells was rescued almost completely by pharmacological inhibition of GSK3 (Sacco et al. 2019)
Antioxidant enzymes (SOD, GPX, catalase)	ROS detoxification	Indirect role	Controversial role	Yes; reduction of ROS	β-cell-specific antioxidant modulation altered susceptibility to diabetogenic injury (Lei and Vatamaniuk 2011)

catalase and thioredoxin have been reported to protect β-cells against streptozotocin (STZ) and/or alloxan treatment in mice (Lei and Vatamaniuk 2011). In sharp contrast, global expression of GPX1 resulted in the development of diabetes (Lei and Vatamaniuk 2011). Knockout of catalase, GPX1, and SOD1 decreased β-cell mass. However, one report showed that GPX1 knockout enhanced tolerance to high-fat diet-induced insulin resistance in mice (Loh et al. 2009). The genetic data seemed to relate to the physiological role of ROS in β-cells.

Two receptors are implicated in β-cell homeostasis, P2Y1 and S1P receptors. P2Y1, also known as P2RY1, is a member of a family of purinergic receptors comprising eight P2Y receptors, which are a class of G protein-coupled receptors (GPCR) (Marcheva et al. 2022). Among them, P2Y1, P2Y6, and P2Y13 were found to be present in mouse β-cells, while P2Y2, P2Y11, and P2Y14 have been found to be expressed in human β-cells (Mesto et al. 2022). Notably, P2Y receptors are thought to participate in β-cell functional plasticity (Mesto et al. 2022). Furthermore, P2Y1 was implicated in insulin secretion and calcium influx (P2Y1, Figure 5) (Marcheva et al. 2022). In contrast, S1P receptors, consisting of five S1P receptor members, are a class of GPCR that are expressed in endothelial cells, the brain, dendritic cells, and so on (Rivera et al. 2008). S1P receptors are well-known for their role in immunity (Rivera et al. 2008). Unluckily, nothing is known about which S1P receptor is expressed in β-cells. However, S1P was documented to increase β-cell proliferation and decrease β-cell death in STZ-treated mice (Y. He et al. 2019). The mode of action of S1P was shown to involve the blockade of voltage-dependent K^+ channels in β-cells (Q. He et al. 2021). Similarly, a synthetic S1P analog, fingolimod, increased β-cell regeneration in db/db mice and β-cell function in diabetic macaques (Y. J. Wang et al. 2022). The data from S1P and its analog suggest the implication of S1P receptors in enhancing β-cell mass and function though no evidence indicated the role of S1P receptors in β-cells (S1P, Figure 5).

TEAD1 is a transcriptional factor that is broadly expressed across tissues such as the pancreas, muscle, placenta, lung, heart, etc. (J. Lee et al. 2024). One report revealed that TEAD1 promoted adult β-cell mature identity, proliferation, and function (J. Lee et al. 2024). The mode of action of TEAD1 could be ascribed to the upregulation of PDX1, NKX6.1, and MAF (TEAD1, Figure 5) (J. Lee et al. 2024).

SIRT1 was initially identified as a NAD-dependent deacetylase (Rahman and Islam 2011). SIRT1 possesses various biological functions implicated in inflammation, oxidative stress, metabolism and aging (Rahman and Islam 2011). Two studies have reported that overexpression of SIRT1 protected against inflammatory cytokine-induced cell death in INS-1 β-cells (J. H. Lee et al. 2009; Wu et al. 2012). Consistently, the SIRT1 activator, resveratrol, also conferred β-cell protection (Wu et al. 2012). In contrast, SIRT1 knockdown lost this protection (Wu et al. 2012). In sharp contrast, MST1, BACH2, PHLPP1 and PDIA4 reduced β-cell death. MST1, a serine/threonine kinase, was reported to be ubiquitously expressed across different cell types in which β-cells are included (Ardestani and Maedler 2016). Diabetogenic stimuli were able to regulate the activation of MST1 in β-cells (MST1, Figure 5). The literature suggests that activated MST1 triggers the release of cytochrome C and mitochondrial apoptotic pathways, leading to caspase 9 and caspase 3 activation, and cell death in β-cells (Ardestani and Maedler 2016; Ardestani et al. 2014). On the other hand, caspase 3 cleaves MST1 into cMST1, which can phosphorylate PDX1. Phosphorylated PDX1 is ubiquitinylated and degraded by proteosomes (Ardestani and Maedler 2016).

BACH2 is a basic leucine zipper transcription factor linked to genetic risk for the development of type 1 diabetes (T1D) (Marroqui et al. 2014). Little is known about the cell distribution of BACH2. However, it was expressed in immune cells and β-cells. Furthermore, BACH2 expression was found to be upregulated by inflammatory cytokines (Marroqui et al. 2014). Notably, the genetic knockdown of BACH2 increased inflammatory cytokine-induced apoptosis in β-cell lines. Briefly, inflammatory cytokines were found to activate the TNF receptor-associated factor 6 (TRAF6)/transforming growth factor β-activated kinase 1 (TAK1)/mitogen-activated protein kinase kinase 7 (MKK7)/c-Jun N-terminal kinases 1 (JNK1) cascade. As a result, JNK1 increased mitochondrion-mediated cell death in β-cells (Son et al. 2021). BACH2 was shown to inhibit MKK7 activation and upregulate PTPN2. On the other hand, PTPN2 dephosphorylated and inactivated JNK1 (BACH2, Figure 5). The above results suggested that BACH2 protected β-cells from death in the milieu of inflammatory cytokines in T1D. In contrast, BACH2 knockout in T2D islets was shown to reverse T2D in the T2D mouse model db/db (Son et al. 2021). BACH2 could form a heterodimer with MAF to bind to the MAF recognition element (MARE), thereby repressing transcription of antioxidant enzymes and, in turn, impairing human β-cells. In contrast, during the inactivation of BACH2, NRF2 was able to bind to the MARE and, subsequently, turned on antioxidant enzyme expression, which is required for β-cell function (Son et al. 2021). Overall, BACH2 mediates β-cell apoptosis in T2D (BACH2, Figure 5). The part played by BACH2 in β-cell protection in different mouse models is controversial and warrants further elucidation.

PHLPP1 belongs to the PHLPP family of phosphatases (Xia et al. 2023). The literature proposes that PHLPP1 is a novel therapeutic target for diabetes (Lupse et al. 2022). Lupse et al. reported that PHLPP1 deletion could rescue pancreatic β-cell survival and normoglycemia in db/db mice (Lupse et al. 2022). Mechanistically, PHLPP1 was shown to dephosphorylate AKT and MST1, which control β-cell viability (PHLPP1, Figure 5).

PDIA4, one of the PDI family, possesses three active (GCHC) domains with oxidoreductase, isomerase and foldase activities. PDIA4 is primarily expressed in β-cells with upregulation in these cells and the sera of rodents reported following nutrient overload (Kuo, Hsu, et al. 2021). Since redox is a key determinant of β-cell fate (Benakova et al. 2021), ROS homeostasis is crucial to β-cell life and death. Genetics data from PDIA4 knockout and transgenic mice illustrated that PDIA4 increased β-cell failure, including cell death and dysfunction, and diabetes due to an increase in ROS as shown by fasting blood glucose (FBG), postprandial blood glucose (PBG), glycosylated hemoglobulin A1c (Hb_{A1c}), glucose tolerance test (GTT), islet architecture, diabetic incidence, and homeostatic model assessment for β-cell function and insulin resistance (HOMA) indices. From

the perspective of the mechanisms involved, PDIA4 augmented the production of ROS in β-cells by the interplay and activation of Ndufs3 and p22 in the ETC complex 1 (ETC C1) and Nox pathways, respectively (PDIA4, Figure 5) (Kuo, Hsu, et al. 2021). Likewise, pharmacological inhibition of PDIA4 slowed ROS production, preserved β-cell function, and improved diabetic symptoms. This important publication clearly showed that PDIA4 is a new molecular target in β-cell pathogenesis and diabetes that acts through ROS dysregulation (Kuo, Hsu, et al. 2021). Regarding potential clinical applications, Chien et al. (C. Y. Chien et al. 2017) found that serum PDIA4 levels were significantly higher in Chinese adults with metabolic syndrome (MetS) in comparison to those without MetS. The study demonstrated that higher PDIA4 levels were connected to increased risks of several MetS components, such as waist circumference, blood pressure, fasting glucose, and triglyceride levels. This association suggests that PDIA4 could serve as a biomarker for MetS and its components, further emphasizing its relevance in MetS.

5 | Preclinical and Clinical Studies of Medicinal Plants and Natural Compounds at the Molecular, Cellular, and Animal Levels

The preservation of β-cell number and function is a promising therapeutic avenue for curing diabetes, shifting the focus from glucose-centered approaches to maintaining the health and functionality of β-cells. Given the impact of the genes and pathways implicated in β-cell homeostasis, natural compounds that target these genes and pathways may be beneficial for diabetes treatment. Such natural compounds include (iso)flavonoids, aliphatic amino alcohols, alkaloids, polyynes, and phenolics as delineated in Table 2 and Figure 6. The listed natural products are often found in fruits, vegetables, beverages, spices, and herbs used in cooking.

5.1 | Flavonoids and Isoflavonoids

Flavonoids are abundant secondary metabolites with different bioactivities that are found in edible fruits, vegetables, and plants. Silymarin, composed of six primarily flavonoids, is an extract of milk thistle seeds used for liver protection. Studies showed that silybin, an active flavonoid of silymarin, could reverse hyperglycemia and repair malfunctioning pancreatic β-cells by upregulating SIRT1 expression in streptozotocin-treated mice, a model of T1D (Q. Wang et al. 2012; Dinić et al. 2024). Another piece of research suggested that silymarin promoted the proliferation of insulin-producing β-cells by increasing the expression of pancreatic Pdx1 transcription factor and β-cell neogenesis (Soto et al. 2014).

Tamarind seeds, which are rich in flavonoids, were shown to selectively increase GLUT2 and GLUT4 levels, and intracellular calcium in β-cells when used as an aqueous extract (Maiti et al. 2005; Sole and Srinivasan 2012). Moreover, tamarind seeds were found to stimulate β-cell proliferation. Consequently, they improved glucose homeostasis in STZ-treated rats, a T1D rodent model (Maiti et al. 2005; Sole and Srinivasan 2012). Treatment with tamarind seed extract increased the glucose transporter 2 (GLUT-2) and sterol regulatory element-binding protein 1c (SREBP1c) mRNA expression. These are both involved in the preservation and neogenesis of β-cells. This extract also displayed insulin-mimetic potential (Costa et al. 2022), mediated by an increase in cytosolic calcium of pancreatic islets. Collectively, tamarind seeds and their flavonoids may reveal new mechanisms through which to achieve β-cell protection and T1D improvement (Maiti et al. 2005; Sole and Srinivasan 2012; Costa et al. 2022).

Quercetin is a very common flavonoid that is present in many fruits, vegetables, and grains. It was found to increase insulin secretion and reduce cell death in β-cells (Zhuang et al. 2023; Oh 2015). Interestingly, it was reported to slightly inhibit PDIA4 (Lin et al. 2015). PDIA4 inhibition is known to reduce β-cell failure (Kuo, Hsu, et al. 2021). Genistein is an isoflavone abundant in soybeans. A high dose of genistein was shown to induce β-cell death. Nonetheless, a low dose of genistein induced cell proliferation and reduced death in β-cells (Oh 2015). Nevertheless, its mode of action is unclear and needs to be ascertained (Smoak et al. 2021).

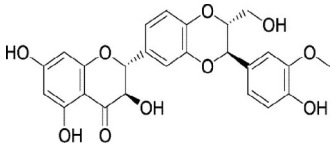
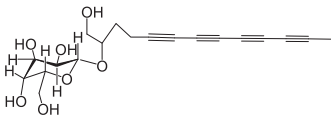
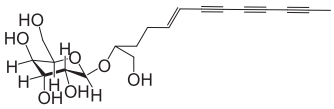
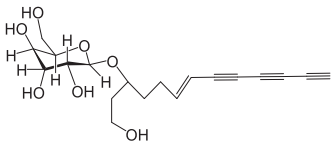
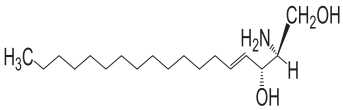
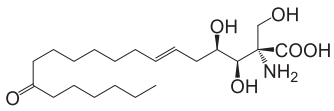
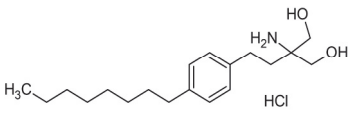
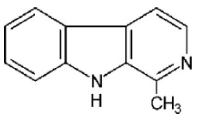
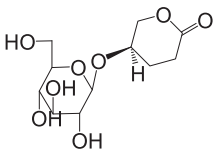
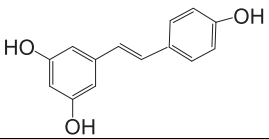
5.2 | Aliphatic Amino Alcohols

S1P is an essential sphingolipid component found in most foods. It acts as a cognate ligand for the S1P receptors. He et al. reported that S1P promoted β-cell proliferation in db/db mouse islets (Liu et al. 2021; Y. He et al. 2019). Similarly, fingolimod (FTY720) is one semi-synthetic derivative of S1P (Adachi and Chiba 2007). Fingolimod has been documented to promote the increase of β-cells in db/db mouse islets and β-cell function in diabetic macaques (Y. J. Wang et al. 2022). In contrast, myriocin, also known as ISP-1 or thermozymocidin, is an S1P derivative present in a medicinal fungus, *Ophiocordyceps sinensis*. This compound was shown to inhibit oleate-induced β-cell proliferation (Castell et al. 2022). It was hypothesized that myriocin is an antagonist of S1P for their receptors.

5.3 | Alkaloids

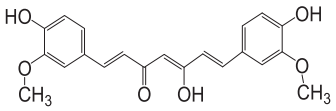
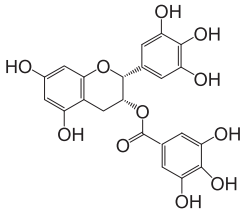
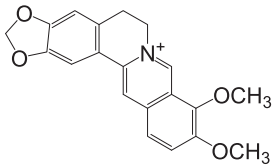
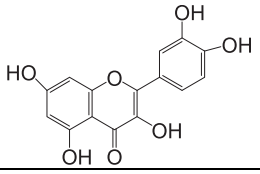
An alkaloid, harmine, was identified in the medicinal plant *Peganum harmala* (Nitrariaceae) as having anti-diabetic and other activities (Asgarpanah and Ramezanloo 2012). It serves as a natural inhibitor of dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) (Adayev et al. 2011). Furthermore, the inhibition of DYRK1A prompted β-cells to multiply (Adayev et al. 2011). Consistently, harmine has been demonstrated to stimulate β-cell proliferation in islets grafted under the kidney capsules of NSG mice (P. Wang et al. 2015; Dirice et al. 2016). Harmine, combined with exendin 4, has been shown to expand human β-cell mass in mouse xenografts (Rosselot et al. 2024). The mechanism by which harmine impacts diabetes is likely the inhibition of DYRK1A, which enhances β-cell apoptosis and dysfunction (Lu et al. 2019). How berberine affects insulin secretion remains contradictory. Long-term treatment with berberine elevates insulin secretion in β-cells and islets, whereas acute treatment inhibits insulin

TABLE 2 | List of natural products that target the proteins that control β-cell homeostasis.

SN	Compound	Protein targeted	Structure	Class	Function	Reference
1	Silybin (silibinin)	SIRT1		Flavonoid	Inhibition of β-cell death	In vivo studies (Dinić et al. 2024; Q. Wang et al. 2012) In vitro study (Du et al. 2023)
2	Silymarin	SIRT1*	—	Flavonoid	Promotion of β-cell proliferation	In vivo/in vitro studies (Soto et al. 2014; Smoak et al. 2021)
3	Tamarind seed extract	—	—	—	Promotion of β-cell proliferation	In vivo *study* (Maiti et al. 2005; Sole and Srinivasan 2012; Costa et al. 2022)
4	Cytopiloyne (2-β-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne)	PDIA4		Polyyne	Inhibition of β-cell failure	In vivo/in vitro studies (Kuo, Hsu, et al. 2021; S. C. Chien et al. 2009)
5	2-β-D-Glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne	PDIA4		Polyyne	Inhibition of β-cell failure	In vivo/in vitro studies (Kuo, Hsu, et al. 2021; S. C. Chien et al. 2009)
6	3-β-D-Glucopyranosyloxy-1-hydroxy-6(E)-tridecene-8,10,12-triyne	PDIA4		Polyyne	Inhibition of β-cell failure	In vivo/in vitro studies (Kuo, Hsu, et al. 2021; S. C. Chien et al. 2009)
7	Sphingosine	S1P receptor		Aliphatic amino alcohol	Promotion of β-cell function and proliferation	In vivo/in vitro studies (Liu et al. 2021; S. C. Chien et al. 2009)
8	Myriocin (ISP-1, thermozymocidin)	S1P receptor		Aliphatic amino alcohol	Inhibition of oleate-induced β-cell proliferation	In vivo/in vitro studies (Castell et al. 2022)
9	Fingolimod (FTY720)	S1P receptor		Aliphatic amino alcohol	Promotion of β-cell function and proliferation	In vivo/in vitro studies (Y. J. Wang et al. 2022)
10	Harmine	DYRK1A		Alkaloid	Promotion of β-cell function and proliferation	In vivo/in vitro studies (Rosselot et al. 2024) In vitro studies (Adayev et al. 2011)
11	Kinsenoside	—		Phenolics	β-cell regeneration	In vivo/in vitro studies (Smoak et al. 2021)
12	Resveratrol	SIRT1		Phenolics	Promotion of β-cell protection	In vivo/in vitro studies (Smoak et al. 2021; Wu et al. 2012)

(Continues)

TABLE 2 | (Continued)

SN	Compound	Protein targeted	Structure	Class	Function	Reference
13	Curcumin	—		Phenolics	Increased β-cell function	In vivo study (Duan et al. 2022) In vitro study (Cao et al. 2022)
14	Epigallocatechin 3-gallate (EGCG)	—		Phenolics	Reduced β-cell death	In vivo/in vitro studies (Y. Shao et al. 2024; Jia et al. 2024)
15	Berberine	—		Alkaloid	Enhanced insulin secretion	In vivo/in vitro studies (Zhao et al. 2021; Lv et al. 2021)
16	Quercetin	PDIA4*		Flavonoid	Promotion of β-cell function and protection	In vivo/in vitro studies (Lin et al. 2015; Zhuang et al. 2023; Dhanya and Kartha 2021)

Note: —, not determined; *, need to be confirmed.

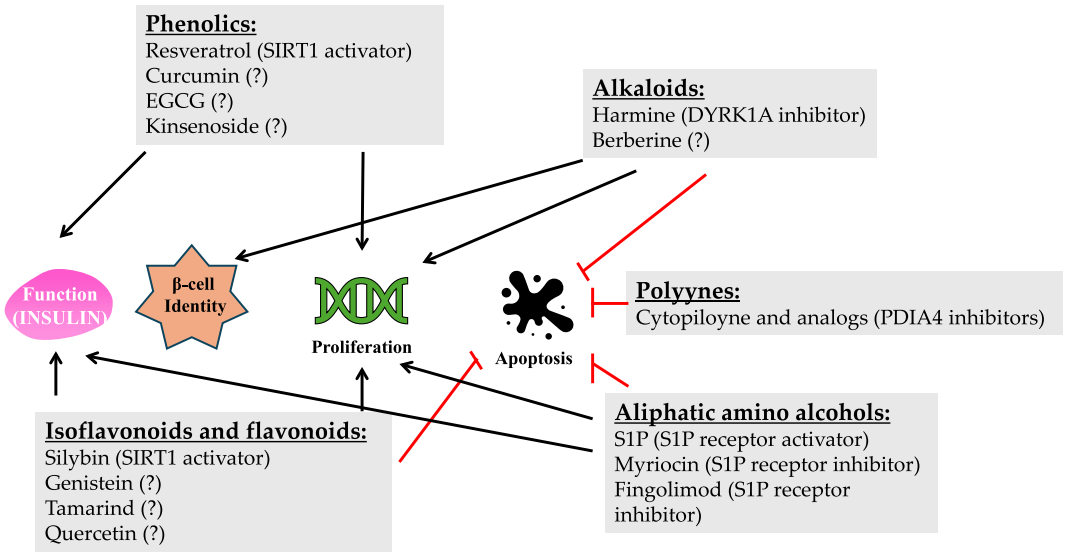


FIGURE 6 | Mechanisms of action of natural compounds that target β-cell identity, function, proliferation, and death. Natural products are classified into groups based on their chemical structures. The functions and/or molecular targets of each natural compound are indicated. The black arrows and red lines denote promotion and inhibition, respectively. Unknown molecular targets are indicated by a question mark.

secretion. Nonetheless, berberine improved diabetes in db/db and STZ-treated mice. Unexpectedly, 3 months of berberine monotherapy in T2D patients resulted in weight loss but did not alleviate hyperglycemia (Oh 2015). The mechanism through which berberine affects β-cells remains to be elucidated.

5.4 | Polyynes

Reactive oxygen species (ROS) are crucial signaling molecules in β-cells (Trachootham et al. 2009). In diabetes, inflammation, excess nutrients, and ER stress cause ROS overproduction in β-cells and other cells (Robertson 2004; Robertson et al. 2004).

As a result, exuberant ROS induce the dysfunction and death of β-cells (Newsholme et al. 2012; Weaver et al. 2015), peripheral insulin resistance (Evans et al. 2005), and complications in both humans and animals with diabetes. One Asteraceae herb, *Bidens pilosa*, is often used as a treatment for diabetes in Asia, America, and Africa (Kuo, Yang, et al. 2021). Over 300 phytochemicals have been identified from this plant (Kuo, Yang, et al. 2021). *B. pilosa* is an unprecedented source of polyynes, including cytopiloyne and its two derivatives. *B. pilosa* and its three polyynes show ameliorative activity in animals with diabetes (Shiau et al. 2015; Yang 2014) and humans (Lai et al. 2015). Notably, cytopiloyne has also been revealed as a natural inhibitor of PDIA4 (Kuo, Hsu, et al. 2021). This inhibitor decreased ROS production, preserved β-cell function, and alleviated diabetic symptoms in mouse models of diabetes (Kuo, Hsu, et al. 2021). Mechanistically, PDIA4 was reported to be associated with Ndufs3 and p22, enhancing ROS generation in both the mitochondria and cytosol of β-cells, respectively. The increased ROS production led to β-cell dysfunction and death, contributing to the progression of diabetes (Kuo, Hsu, et al. 2021). Ndufs3 and p22 are key players in the electron transport chain complex 1 (ETC C1) and NADPH oxidase (NOX) pathways, respectively. Conversely, cytopiloyne abolished the interaction between PDIA4 and Ndufs3, and p22, and subsequently diminished the production of mitochondrial and cytosolic ROS in β-cells (Kuo, Hsu, et al. 2021). A PDIA4 inhibitor, PS1 ($C_{12}H_{11}NO_5$), was developed as a drug candidate using molecular docking and chemical synthesis (Tseng et al. 2023). In db/db mice, PS1 alone or used with metformin, a first-line OAA, was demonstrated to reverse diabetes by 60% and 100%, respectively. This seminal work showed that PS1 could treat and reverse diabetes via PDIA4-mediated ROS production disruption. PS1 action was evidenced by blood glucose maintenance, β-cell function and structure, survival rate, and longevity in diabetic mouse models (Tseng et al. 2023). In addition, PS1 was found to be more effective than cytopiloyne, leading to obvious improvements in diabetes and β-cell pathogenesis without side effects. Currently, PS1 is on a clinical trial (https://clinicaltrials.gov/study/NCT05176210?cond=PS1&rank=2). The mechanism of PDIA4 and its inhibitors are depicted in Figures 5 and 6, respectively. Pharmacological inhibition of PDIA4 can improve the survival and function of β-cells, as well as glucose homeostasis, offering a therapeutic opportunity for diabetes management.

5.5 | Phenolics

Fruits, vegetables, beverages (wines, coffee, tea, cocoa, etc.), spices, and culinary herbs are excellent sources of dietary phenolics for humans. Resveratrol, rich in red wines, has been documented to have multiple beneficial functions (Wu et al. 2012; Smoak et al. 2021). Notably, it was reported to activate SIRT1, which is responsible for β-cell protection (J. H. Lee et al. 2009; Wu et al. 2012). Curcumin, a major constituent of *Curcuma longa* (Duan et al. 2022; Cao et al. 2022), and epigallocatechin 3-gallate (EGCG), an active phytochemical in tea (Y. Shao et al. 2024; Jia et al. 2024), improve β-cell function and reduce β-cell death, respectively (Smoak et al. 2021). Kinsenoside, a phenolic compound derived from *Anoectochilus roxburghii*, was indicated to improve diabetes in STZ-treated mice. Its action involved β-cell regeneration (Smoak et al. 2021).

6 | Strengths and Weaknesses of Using Medicinal Plants and Natural Compounds in Diabetes Management

Many drug leads are derived from natural products. They offer distinct advantages in drug discovery owing to their diverse structures and abilities to modulate multiple signaling pathways related to β-cell identity, function, and growth. These compounds are already available in our diets and are cost-effective for use in our daily lives (Singh et al. 2025). Furthermore, the compounds can be absorbed via the gut with few side effects. Identification of new compounds could assist in the development of new drugs and diabetes therapies. For instance, polyynes in *B. pilosa* have been used as herbal medicines and nutraceuticals for treating and reversing diabetes (Lai et al. 2015). The molecular target of the polyynes was identified as PDIA4, a novel target (Kuo, Hsu, et al. 2021). Using a combination of molecular docking, chemical modification/synthesis, and bioassays, PDIA4-targeted drug candidates can be developed for clinical trials (Tseng et al. 2023).

Despite the above benefits, several challenges associated with natural compounds need to be addressed, such as their pharmacokinetics, toxicity, total synthesis, efficacy, stability, and target identification. Toxicity, total synthesis, efficacy, and the stability of natural compounds are issues that need to be overcome prior to their clinical trials, and these challenges are sometimes not easy to address. For example, the molecular targets of half of the natural products discussed in the studies (Table 2) are not fully identified. The literature reports 1200 medicinal plants with anti-diabetic activities. Their successful clinical application will face additional challenges, including the high complexity of phytochemicals and issues with quality control and batch consistency. To date, only two botanical drugs have been approved. Therefore, from the current regulatory perspective, the use of medicinal plants as nutraceuticals is easier than their use as drugs, although the former mainly target "sub-healthy" people with sub-clinical symptoms, whereas the latter target patients who are clinically sick. Additionally, the pharmacokinetic properties (low bioavailability, rapid metabolism, and suboptimal absorption in the intestines) of natural products frequently pose challenges for their clinical application.

7 | Challenges and Future Directions

Pancreatic β-cells are central to the development and treatment of diabetes. Emerging technologies, such as single-cell transcriptomics, CRISPR gene editing, and selective screening for molecules of β-cells through metabolomics, serve as powerful tools to uncover significance of novel genes related to β-cell function and mass. Furthermore, out of 1200 anti-diabetic plants, 16 natural compounds have been documented to act on β-cells. Although those compounds are known to reduce β-cell failure

and even increase β-cell mass and function, the effects of the natural products as agents for β-cell preservation and diabetes management are limited and sometimes inconclusive. In fact, some results are contradictory. For example, it is not clear whether genistein at low and high dosages had opposite outcomes in β-cells (Oh 2015). Moreover, molecular targets of several natural products, such as BACH2, DYRK1A, and antioxidant enzymes for β-cell pathogenesis and diabetes, are dichotomous across different experimental systems. Furthermore, although 16 natural compounds and 13 types of molecular targets have been reported to modulate β-cells, barring a few (PDIA4, PDX1, NKX6.1 and so on), most of these molecular targets are ubiquitously expressed. Therefore, the specificity and target identification of compounds in β-cells and other tissues need to be verified before further nutraceutical applications for diabetes management can be developed. In addition, the pharmacokinetic challenges of these compounds need to be addressed. The development of targeted delivery systems, such as exosomes, liposomes, or hydrogels, might be valuable for the clinical application of natural products (Zhuang et al. 2023; Dinić et al. 2024). Nevertheless, β-cell-specific molecular targeting systems need to be considered, and no such systems have been reported so far. It is also worth combining existing OAA or incretins with natural compounds that act through different mechanisms to improve efficacy and reduce side effects.

8 | Conclusion

This review discusses the critical role of proteins implicated in β-cell preservation and diabetes comprehensively, highlighting their emerging potential as therapeutic targets. By detailing the molecular basis through which these targets dictate diabetes progression and pharmacological efficacy, and the mechanisms of these natural compounds, this work reveals the potential of these activators and/or inhibitors for developing novel therapeutic strategies to treat and cure diabetes. Their mechanisms involve regulation of the life and death, (re)generation, and functionalities of β-cells. Moreover, the overview of therapeutic targets and their modulators at the molecular, cellular, and organismic levels presented herein can serve as guidance for the research and development of pharmaceuticals and/or nutraceuticals for diabetes.

Notwithstanding, some limitations of current research into the proteins and their compounds were noted herein. For example, insufficient understanding of the proteins, lack of clinical trials of natural products, incomplete chemistry, manufacturing, and controls, and the lack of optimization of delivery systems for natural products are issues that need to be addressed in human-based studies.

Author Contributions

Yi-San Lee: writing – original draft, data curation, conceptualization, software. **Tien-Fen Kuo:** writing – editing draft, investigation. **Chun-Yen Yang:** writing – editing draft, data curation. **Greta Yang:** writing – editing draft, data curation. **Wen-Chin Yang:** conceptualization, writing – review and editing, funding acquisition, supervision.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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